



Attorney's Docket No. 033053-025
Patent

AF/1616

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of)
Kenneth C. CUNDY et al.) Group Art Unit: 1616
Application No.: 09/972,425) Examiner: Barara Radio
Filed: October 5, 2001) Confirmation No.: 5701
For: BILE-ACID DERIVED COMPOUNDS FOR)
PROVIDING SUSTAINED SYSTEMIC)
CONCENTRATIONS OF DRUGS AFTER)
ORAL ADMINISTRATION)

TRANSMITTAL LETTER

Assistant Commissioner for Patents
Washington, D.C. 20231
PETITION BRANCH

Sir:

These documents are submitted in order to Petition the Commissioner to Withdraw
Requirement for Restriction Under 37 CFR §§ 1.144 and 1.181

Enclosed please find:

Petition from Requirement for Restriction under 37 CFR §§ 1.144 and 1.181

A Petition for One Month Extension of Time.

The Commissioner is hereby authorized to charge any appropriate fees under 37 C.F.R.
§§ 1.16, 1.17 and 1.21 that may be required by this paper, and to credit any overpayment, to
Deposit Account No. 02-4800. This paper is submitted in triplicate.

Respectfully submitted,

BURNS, DOANE, SWECKER & MATHIS, L.L.P.

P.O. Box 1404
Alexandria, Virginia 22313-1404
(703) 836-6620

By: Melissa M. Hayworth
Melissa M. Hayworth
Registration No. 45,774

Date: December 29, 2003



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FOR PROVIDING SUSTAINED)
SYSTEMIC CONCENTRATIONS OF)
DRUGS AFTER ORAL)
ADMINISTRATION)

**PETITION FROM REQUIREMENT FOR RESTRICTION
UNDER 37 C.F.R. §§ 1.144 AND 1.181**

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

Applicants hereby petition the Commissioner under the provisions of 37 C.F.R. §§ 1.144 and 1.181 to review and withdraw the restriction requirement maintained in the above-identified patent application.

The above-identified application claims novel bile acid GABA analogs, pharmaceutical compositions comprising these compounds, methods of achieving sustained therapeutic or prophylactic blood concentrations of these compounds, and methods of treatment using these compounds. The application includes 41 Examples of synthesis of 132 compounds, which are within the claims as originally filed. A copy of claim 1, directed to a method of achieving sustained concentrations, and claim 5, directed to a compound of formula I, as originally filed, as well as claim 1 and claim 5 as amended in a response filed on August 4, 2003, are attached in Appendix A, for the Commissioner's convenience.

Petitioner notes that a first election of species requirement was issued on January 15, 2003. This requirement was traversed in a response filed on March 17, 2003. The election of species requirement and the generic group as defined by the Examiner was repeated and made final in the Office Action mailed on September 29, 2003. As required by 37 C.F.R. § 1.144, reconsideration of the restriction/election of species requirement has been requested and this requirement has been repeated and made final.

As required by 37 C.F.R. §1.181(b), below is a *Statement of Facts, Points to be Reviewed and Action Requested.*

STATEMENT OF FACTS:

The Examiner issued an election of species requirement on January 15, 2003 stating that the application contained claims directed to more than one species of the generic invention. The action further asserted that due to the number of combinations of variables involved in the claims and their widely divergent meaning, a precise listing of inventive groups cannot be made. The action requested the Applicants to elect a single disclosed species from under the instant claims. The action stated that with the election of a specific species, the Examiner would then build a generic concept if possible as the inventive group for examination.

Applicants filed a response on March 17, 2003, electing the species identified by compound 230 and reserving the right to traverse any subsequent divisions made by the Examiner into "inventive groups." Applicants identified claims 1 – 10, 19, and 20 as reading on the elected species.

The Examiner issued a non-final office action on May 2, 2003, acknowledging election of the species identified by compound 230. Based on the election, the Examiner indicated that the following generic concept would be examined: compounds of formula (I) wherein:

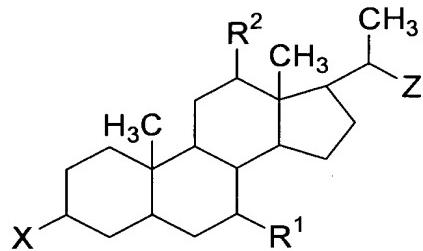
- (a) X is hydroxyl;
- (b) R¹ and R² are independently hydrogen or hydroxyl; and
- (c) Z is a group of the formula –M-Q^b-D' wherein

M is -CH₂OC(O) or -CH₂CH₂C(O)-;

Q^b is -[E-(F*)_nG]- where E is -O-, G is -C(O), and F is as defined by claim 8;
and

D' is a GABA analog moiety as defined by claim 5 wherein R^{3'} is a bond linking the GABA analog moiety to Q^b and R^{11'} is selected from the group consisting of carboxylic acid, carboxylic amide, and carboxylic ester.

Applicants filed a response on August 4, 2003, amending the claims to recite a compound of formula (I) as follows:



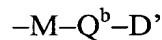
(I)

wherein:

R¹ and R² are independently hydrogen or hydroxy;

X is hydroxy;

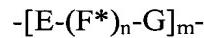
Z is a group of the formula:



wherein:

M is selected from the group consisting of $-\text{CH}_2\text{OC(O)}-$ and $-\text{CH}_2\text{CH}_2\text{C(O)}-$;

Q^b is a covalent bond or a linking group of formula:



wherein:

m is an integer of from 1 to 4;

n is 0 or 1;

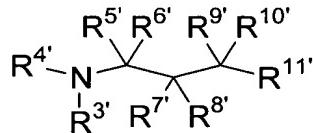
E is $-\text{NH-}$ or $-\text{O-}$;

F* is selected from a group consisting of alkylene, substituted alkylene, alkenylene, substituted alkenylene, alkynylene, substituted alkynylene, cycloalkylene, substituted cycloalkylene, cycloalkenylene, substituted cycloalkenylene, arylene, substituted arylene, heteroarylene, substituted heteroarylene, heterocyclene and substituted heterocyclene; and

G is $-\text{OC(O)-}$, $-\text{C(O)-}$, or $-\text{NH-}$;

wherein Q^b is cleavable under physiological conditions provided that Q^b is not a linear oligopeptide consisting of 1, 2 or 3 α -amino acids and/or β -amino acids; and

D' is a GABA analog moiety of the formula:



wherein:

R^{3'} is a covalent bond linking the GABA analog moiety to Q^b;

R^{4'} is hydrogen or R^{4'} and R^{9'} together with the atoms to which they are attached form a heterocyclic ring;

R^{5'} and R^{6'} are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, aryl, substituted aryl, heteroaryl and substituted heteroaryl;

R^{7'} and R^{8'} are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, alkynyl, aryl, substituted aryl, heteroaryl and substituted heteroaryl, or R^{7'} and R^{8'} together with the atoms to which they are attached form a cycloalkyl, substituted cycloalkyl, heterocyclic or substituted heterocyclic ring;

R^{9'} is selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, alkynyl, aryl, substituted aryl, heteroaryl and substituted heteroaryl;

R^{10'} is selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, alkynyl, aryl, substituted aryl, heteroaryl and substituted heteroaryl;

R^{11'} is selected from the group consisting of carboxylic acid, carboxylic amide, carboxylic ester, sulfonamide, phosphonic acid, acidic heterocycle, sulfonic acid, and hydroxamic acid; or

a pharmaceutically acceptable salt thereof.

Accordingly, the compounds as claimed include a bile acid moiety linked by a group of formula –M–Q^b– to a GABA moiety D'.

Applicants maintained and continue to maintain that compounds, as defined above, clearly evidence unity of invention and define a group of compounds that can be readily searched.

In the response filed, Applicants argued that through the identification of the “inventive group” as defined by the Examiner, the Examiner is requiring the dissection of Applicants’ invention into countless groups, and the Examiner, rather than the Applicants, is identifying what Applicants regard as their invention. Accordingly, Applicants argued that the election requirement coupled with the generic group, as defined by the Examiner, necessitates the dissection of Applicants’ invention into numerous groups and constitutes a refusal on the part of the Office to examine the claim that Applicants believe to best represent their invention. Applicants submitted that it is improper for the Office to refuse to examine that which Applicants regard as their invention unless the subject matter of the claims lacks unity of invention. Unity of invention exists where compounds included within a Markush group (1) share a common utility and (2) share a substantial structural feature.

Applicants submitted that with regard to a common utility, the compounds of the presently claimed invention use the bile acid transport system to provide sustained systemic concentration of orally delivered GABA analogs. With regard to a substantial structural feature, the compounds as presently claimed all comprise a bile acid moiety linked by a linker group to a GABA analog moiety. Applicants further submitted that the precise structure of the linker group connecting the bile acid moiety and the GABA analog moiety is not critical; it is only necessary that the linking group be cleavable under physiological conditions to release the GABA analog moiety or active metabolite thereof into the systemic blood circulation. Therefore, Applicants submitted that the compounds of the present claims clearly evidenced unity of invention, and thus, it was improper for the Office to refuse to examine the presently claimed invention.

Applicants noted that they would be willing to file one or more divisional applications to the non-elected subject matter.

The Examiner issued a final Office Action on September 29, 2003, closing prosecution on the merits and maintaining the dissection of claim 1 into compounds, as defined by the Examiner, wherein:

- (a) X is hydroxyl;
- (b) R¹ and R² are independently hydrogen or hydroxyl; and
- (c) Z is a group of the formula -M-Q^b-D' wherein
 - M is -CH₂OC(O) or -CH₂CH₂C(O)-;
 - Q^b is -[E-(F*)_nG]- where E is -O-, G is -C(O), and F is as defined by claim 8; and
 - D' is a GABA analog moiety as defined by claim 5 wherein R^{3'} is a bond linking the GABA analog moiety Q^b and R^{11'} is selected from the group consisting of carboxylic acid, carboxylic amide, and carboxylic ester.

In the final Office Action, the Examiner indicated that claims 5 – 10 were objected to as containing non-elected inventions but would be allowable to the extent they read on the generic group as defined by the Examiner. The Examiner further indicated that the method claims of the same scope would also be allowable.

It is from this final Office Action which Applicants petition the Commissioner.

POINTS TO BE REVIEWED

Restriction Requirement as Maintained is Improper

Applicants respectfully assert that the restriction/election of species requirement as maintained is improper.

To further prosecution, Applicants amended the pending claims to recite a compound of formula (I) comprising a bile acid moiety linked by a group of formula –M–Q^b– to a GABA moiety D'. Applicants respectfully assert that the claimed compounds as amended clearly exhibit unity of invention.

Applicants submit that it is improper for the Office to refuse to examine that which Applicants regard as their invention when the subject matter of the claims exhibits unity of invention. (MPEP 803.02). Specifically, in *In re Weber*, 580 F.2d 455, 198 USPQ 328 (CCPA 1978), the court articulated the general proposition that:

[A]n applicant has a right to have *each* claim examined on the merits. If an applicant submits a number of claims, it may well be that pursuant to a proper restriction requirement, those claims will be dispersed to a number of applications. Such action would not affect the right of the applicant eventually to have each of the claims examined in the form he considers to best define his invention. If, however, a single claim is required to be divided up and presented in several applications, that claim would never be considered on its merits. The totality of the resulting fragmentary claims would not necessarily be the equivalent of the original claim. Further, since the subgenera would be defined by the examiner rather than by the applicant, it is not inconceivable that a number of the fragments would not be described in the specification.

Id. at 331.

In view of the above and similar case law, the Patent Office has set forth a general policy regarding restriction of Markush-type claims in MPEP 803.02. According to the general policy as articulated in the MPEP, “since the decisions in *In re Weber*, 580 F.2d 455, 198 USPQ 328 (CCPA 1978) and *In re Haas*, 580 F.2d 461, 198 USPQ 334, it is *improper* for the Office to refuse to examine that which applicants regard as their invention, unless the subject matter in a claim lacks unity of invention. *In re Harnish*, 631 F.2d 716, 206 USPQ 300 (CCPA 1980); and *Ex parte Hozumi*, 3 USPQ2d 1059 (Bd. Pat. App. & Int. 1984).” (MPEP 803.02, emphasis added). Unity of invention exists where compounds included within a Markush group (1) share a common utility and (2) share a substantial structural feature. (MPEP 803.02).

Accordingly, Applicants submit that it is improper for the Office to refuse to examine the presently claimed invention since the presently claimed subject matter clearly evidences unity of invention. With regard to a common utility, the compounds of the present invention the compounds of the presently claimed invention use the bile acid transport system to provide sustained systemic concentration of orally delivered GABA analogs. With regard to a substantial structural feature, the compounds as presently claimed all comprise a bile acid moiety linked by a group of formula –M–Q^b– to a GABA moiety D'. The linker group connecting the bile acid moiety and the GABA analog moiety is cleavable under physiological conditions to release the GABA analog moiety or active metabolite thereof into the systemic blood circulation. Applicants respectfully submit that a more precise structure of the linker group is not necessary. The recited structure, as presently claimed, provides a common structural backbone that is a substantial structural feature. This common structural backbone can readily be searched without serious burden. Therefore, Applicants respectfully assert that a refusal on the part of the Office to examine the amended claim presented by Applicants is improper.

Furthermore, Applicants assert that even where a provisional election of a single species is proper prior to examination on the merits, following election the Markush-type claim will be examined fully with respect to the elected species and further to the extent necessary to determine patentability. (MPEP 803.02). The MPEP requires that should no prior art be found that anticipates or renders obvious the elected species, the search of the Markush-type claim *will be extended* to non-elected species. (Id.). The MPEP states that the search need not be extended unnecessarily to cover all non-elected species; however, the MPEP states that Applicant is entitled to consideration of claims to a reasonable number of disclosed species in addition to the elected species. (MPEP 809.02(b)).

Applicants specification includes forty one (41) synthesis examples disclosing the synthesis of 132 compounds within the compound of formula I as originally defined. The definition of the compound of formula I, as amended by Applicants, includes thirty one (31) of Applicants disclosed 132 compounds. The definition of the compound of formula I, that the Examiner has defined and is willing to examine, only includes three (3) of Applicants disclosed 132 compounds (the compounds of Examples 39 and 40 and the compound of Example 38, which was the compound elected). Applicants respectfully submit that three compounds is *not* a reasonable number of disclosed species.

Applicants respectfully submit that the class of compounds that the Examiner has defined is incredibly limited and as such, does not cover a reasonable number of species.

Applicants further assert that this incredibly limited class of compounds is not what Applicants regard as their invention and it is *improper* for the Office to refuse to examine that which Applicants regard as their invention, unless the subject matter in a claim lacks unity of invention. *In re Harnish*, 631 F.2d 716, 206 USPQ 300 (CCPA 1980); and *Ex parte Hozumi*, 3 USPQ2d 1059 (Bd. Pat. App. & Int. 1984)." (MPEP 803.02, emphasis added).

Applicants submit that it is inequitable and unjust for the Examiner to limit Applicants' claim in the manner in which he has done so. If the restriction requirement is maintained, to obtain coverage of the compounds, which Applicants regard as their invention, Applicants will be required to file countless patent applications, thus placing an unreasonable and unjust burden on the Applicants.

ACTION REQUESTED

In view of the foregoing facts and remarks, Applicants request the Commissioner to withdraw the restriction requirement as maintained in the above-identified patent application. Please contact the undersigned at (703) 838-6663 if there are any questions concerning this Petition.

Respectfully submitted,

BURNS, DOANE, SWECKER & MATHIS, L.L.P.

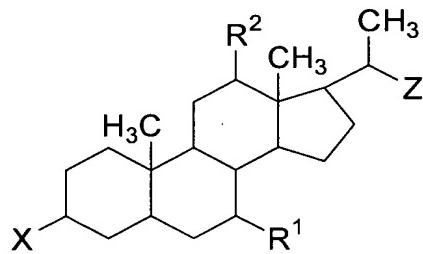
By: Melissa M. Hayworth
Melissa M. Hayworth
Registration No. 45,774

P.O. Box 1404
Alexandria, Virginia 22313-1404
(703) 836-6620

Date: December 29, 2003

APPENDIX A

1. (Originally Filed) A method for achieving sustained therapeutic or prophylactic blood concentrations of a GABA analog or an active metabolite thereof in the systemic circulation of an animal which method comprises orally administering to said animal a compound of formula (I):



(I)

wherein:

R¹ and R² are independently hydrogen or hydroxy;

X is selected from the group consisting of hydroxy and D-Q^a-(T)- wherein:

T is -O- or -NH-;

Q^a is a covalent bond or a linking group that may cleave under physiological conditions to release a GABA analog or active metabolite thereof into the systemic blood circulation of said animal, wherein said linking group is not a linear oligopeptide comprising 1, 2 or 3 α-amino acids and/or β-amino acids; and

D is a GABA analog moiety;

Z is selected from the group consisting of (a) a substituted alkyl group containing a moiety which is negatively charged at physiological pH which moiety is selected from the group consisting of -COOH, -SO₃H, -SO₂H, -P(O)(OR¹⁹)(OH), -OP(O)(OR¹⁹)(OH), -OSO₃H, wherein R¹⁹ is selected from the group consisting of alkyl, substituted alkyl, aryl and substituted aryl; and (b) a group of the formula:

-M-Q^b-D'

wherein:

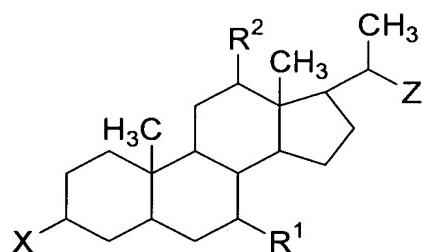
M is selected from the group consisting of $-\text{CH}_2\text{OC(O)}-$ and $-\text{CH}_2\text{CH}_2\text{C(O)}-$;

Q^b is a covalent bond or a linking group which may cleave under physiological conditions to release a GABA analog or active metabolite thereof into the systemic blood circulation of said animal, wherein said linking group is not a linear oligopeptide consisting of 1, 2 or 3 α -amino acids and/or β -amino acids; and

D' is a GABA analog moiety

provided that when X is hydroxy, then Z is a group of the formula $-\text{M}-\text{Q}^b-\text{D}'$.

5. (Originally Filed) A compound of formula (I):



(I)

wherein:

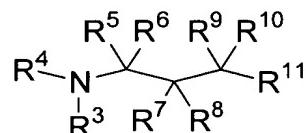
R^1 and R^2 are independently hydrogen or hydroxy;

X is selected from the group consisting of hydroxy and $\text{D}-\text{Q}^a-(\text{T})-$ wherein:

T is $-\text{O}$ or $-\text{NH}-$;

Q^a is a covalent bond or a linking group; and

D is a GABA analog moiety preferably of the formula:



where:

R^3 is selected from the group consisting of hydrogen, an amino-protecting group, or a covalent bond linking the GABA analog moiety to Q^a ;

R^4 is hydrogen, or R^4 and R^9 together with the atoms to which they are attached form a heterocyclic ring;

R^5 and R^6 are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, aryl, substituted aryl, heteroaryl and substituted heteroaryl;

R^7 and R^8 are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, alkynyl, aryl, substituted aryl, heteroaryl and substituted heteroaryl, or R^7 and R^8 together with the atoms to which they are attached form a cycloalkyl, substituted cycloalkyl, heterocyclic or substituted heterocyclic ring;

R^9 is selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, alkynyl, aryl, substituted aryl, heteroaryl and substituted heteroaryl;

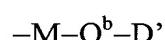
R^{10} is selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, alkynyl, aryl, substituted aryl, heteroaryl and substituted heteroaryl;

R^{11} is selected from the group consisting of carboxylic acid, carboxylic amide, carboxylic ester, sulfonamide, phosphonic acid, acidic heterocycle, sulfonic acid, hydroxamic acid and $C(O)R^{12}$;

R^{12} is a covalent bond linking the GABA analog moiety to Q^a , provided only one of R^3 and R^{12} links D to Q^a ;

Z is selected from the group consisting of (a) a substituted alkyl group containing a moiety which is negatively charged at physiological pH which moiety is selected from the group consisting of $-COOH$, $-SO_3H$, $-SO_2H$, $-P(O)(OR^{19})(OH)$, $-OP(O)(OR^{19})(OH)$, $-OSO_3H$, wherein R^{19} is selected from the group consisting of alkyl, substituted alkyl, aryl and substituted aryl; and

(b) a group of the formula:

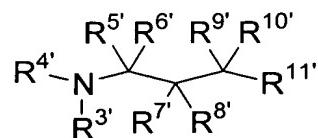


wherein:

M is selected from the group consisting of $-CH_2OC(O)-$ and $-CH_2CH_2C(O)-$;

Q^b is a covalent bond or a linking group which may cleave under physiological conditions to release a GABA analog or active metabolite thereof into the systemic blood circulation of said animal; and

D' is a GABA analog moiety preferably of the formula:



wherein:

R^3' is selected from the group consisting of hydrogen, an amino-protecting group, or a covalent bond linking the GABA analog moiety to Q^b ;

R^4' is hydrogen or R^4' and R^9' together with the atoms to which they are attached form a heterocyclic ring;

R^5' and R^6' are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, aryl, substituted aryl, heteroaryl and substituted heteroaryl;

R^7' and R^8' are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, alkynyl, aryl, substituted aryl, heteroaryl and substituted heteroaryl, or R^7' and R^8' together with the atoms to which they are attached form a cycloalkyl, substituted cycloalkyl, heterocyclic or substituted heterocyclic ring;

R^9' is selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, alkynyl, aryl, substituted aryl, heteroaryl and substituted heteroaryl;

$R^{10'}$ is selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, alkynyl, aryl, substituted aryl, heteroaryl and substituted heteroaryl;

$R^{11'}$ is selected from the group consisting of carboxylic acid, carboxylic amide, carboxylic ester, sulfonamide, phosphonic acid, acidic heterocycle, sulfonic acid, hydroxamic acid and $C(O)R^{12'}$;

$R^{12'}$ is a covalent bond linking the GABA analog moiety to Q^b , provided only one of R^3' and $R^{12'}$ links D to Q^b ; or

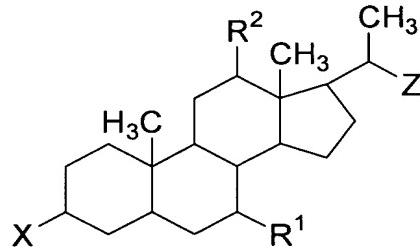
a pharmaceutically acceptable salt thereof;

provided that when X is hydroxy, then Z is a group of the formula $-M-Q^b-D'$; and

further provided that when X is hydroxy, M is $-\text{CH}_2\text{CH}_2\text{C}(\text{O})-$, Q^b is a covalent bond and $R^{11'}$ is carboxylic acid, then at least one of R^5' , R^6' , R^7' , R^8' , R^9' and $R^{10'}$ is other than hydrogen; and

yet further provided that neither Q^a nor Q^b is a linear oligopeptide comprised exclusively of 1, 2 or 3 α -amino acids and/or β -amino acids.

1. (Amended) A method for achieving sustained therapeutic or prophylactic blood concentrations of a GABA analog or an active metabolite thereof in the systemic circulation of an animal which method comprises orally administering to said animal a compound of formula (I):



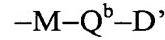
(I)

wherein:

R^1 and R^2 are independently hydrogen or hydroxy;

X is hydroxy;

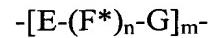
Z is a group of the formula:



wherein:

M is selected from the group consisting of $-\text{CH}_2\text{OC}(\text{O})-$ and $-\text{CH}_2\text{CH}_2\text{C}(\text{O})-$;

Q^b is a covalent bond or a linking group of formula:



wherein:

m is an integer of from 1 to 4;

n is 0 or 1;

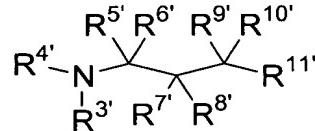
E is $-NH-$ or $-O-$;

F^* is selected from a group consisting of alkylene, substituted alkylene, alkenylene, substituted alkenylene, alkynylene, substituted alkynylene, cycloalkylene, substituted cycloalkylene, cycloalkenylene, substituted cycloalkenylene, arylene, substituted arylene, heteroarylene, substituted heteroarylene, heterocyclene and substituted heterocyclene; and

G is $-OC(O)-$, $-C(O)-$, or $-NH-$;

wherein Q^b is cleavable under physiological conditions provided that Q^b is not a linear oligopeptide consisting of 1, 2 or 3 α -amino acids and/or β -amino acids; and

D' is a GABA analog moiety of the formula:



wherein:

R^3' is a covalent bond linking the GABA analog moiety to Q^b ;

R^4' is hydrogen or R^4' and R^9' together with the atoms to which they are attached form a heterocyclic ring;

R^5' and R^6' are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, aryl, substituted aryl, heteroaryl and substituted heteroaryl;

R^7' and R^8' are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, alkynyl, aryl, substituted aryl, heteroaryl and substituted

heteroaryl, or R⁷ and R⁸ together with the atoms to which they are attached form a cycloalkyl, substituted cycloalkyl, heterocyclic or substituted heterocyclic ring;

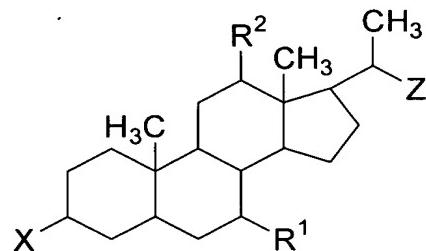
R⁹ is selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, alkynyl, aryl, substituted aryl, heteroaryl and substituted heteroaryl;

R¹⁰ is selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, alkynyl, aryl, substituted aryl, heteroaryl and substituted heteroaryl;

R¹¹ is selected from the group consisting of carboxylic acid, carboxylic amide, carboxylic ester, sulfonamide, phosphonic acid, acidic heterocycle, sulfonic acid, and hydroxamic acid; or

a pharmaceutically acceptable salt thereof.

5. (Amended) A compound of formula (I):



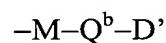
(I)

wherein:

R¹ and R² are independently hydrogen or hydroxy;

X is hydroxy;

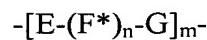
Z is a group of the formula:



wherein:

M is selected from the group consisting of $-\text{CH}_2\text{OC(O)}-$ and $-\text{CH}_2\text{CH}_2\text{C(O)}-$;

Q^b is a covalent bond or a linking group of formula:



wherein:

m is an integer of from 1 to 4;

n is 0 or 1;

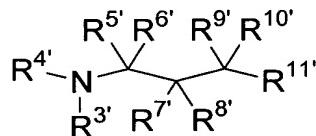
E is -NH- or -O-;

F* is selected from a group consisting of alkylene, substituted alkylene, alkenylene, substituted alkenylene, alkynylene, substituted alkynylene, cycloalkylene, substituted cycloalkylene, cycloalkenylene, substituted cycloalkenylene, arylene, substituted arylene, heteroarylene, substituted heteroarylene, heterocyclene and substituted heterocyclene; and

G is -OC(O)-, -C(O)- or -NH-;

wherein Q^b is cleavable under physiological conditions; and

D' is a GABA analog moiety of the formula:



wherein:

R^{3'} is a covalent bond linking the GABA analog moiety to Q^b;

R^{4'} is hydrogen or R^{4'} and R^{9'} together with the atoms to which they are attached form a heterocyclic ring;

R^{5'} and R^{6'} are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, aryl, substituted aryl, heteroaryl and substituted heteroaryl;

R^{7'} and R^{8'} are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, alkynyl, aryl, substituted aryl, heteroaryl and substituted heteroaryl, or R^{7'} and R^{8'} together with the atoms to which they are attached form a cycloalkyl, substituted cycloalkyl, heterocyclic or substituted heterocyclic ring;

R^{9'} is selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, alkynyl, aryl, substituted aryl, heteroaryl and substituted heteroaryl;

$R^{10'}$ is selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, alkynyl, aryl, substituted aryl, heteroaryl and substituted heteroaryl;

$R^{11'}$ is selected from the group consisting of carboxylic acid, carboxylic amide, carboxylic ester, sulfonamide, phosphonic acid, acidic heterocycle, sulfonic acid, and hydroxamic acid; or

a pharmaceutically acceptable salt thereof;

provided that when X is hydroxy, M is $-CH_2CH_2C(O)-$, Q^b is a covalent bond and $R^{11'}$ is carboxylic acid, then at least one of $R^{5'}$, $R^{6'}$, $R^{7'}$, $R^{8'}$, $R^{9'}$ and $R^{10'}$ is other than hydrogen; and

further provided that Q^b is not a linear oligopeptide comprised exclusively of 1, 2 or 3 α -amino acids and/or β -amino acids.